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Analysis of questionnaire survey to determine worldwide trends in prescriptions of biologics for the treatment of unresponsive chronic urticaria

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ABSTRACT

Background: Chronic spontaneous urticaria (CSU) is a common condition treated by allergist/immunologists, but the only FDA-approved biologic medication, omalizumab, may be underutilized globally.

Objective: This study was performed to determine the global prescription of omalizumab for treatment of CSU by allergists/immunologists.

Methods: Anonymous questionnaire surveys were distributed online to World Allergy Organization (WAO) members worldwide. Categorical data were analyzed for descriptive analysis using one-way frequency tabulation in SAS 9.4.

Results: There were 348 respondents (43 missing data); Average age 51 (range 28–90); M/F 48%/52%. 58% had $>$ 15 years of clinical experience and 10% $<$ 5; 42% worked in private clinics, 36% public hospitals, 24% academia, 18% private hospitals, and 4% in community practice. Eighty-two percent (82%) prescribed omalizumab for CSU patients and use of omalizumab was highest among young practitioners. The most significant barriers were cost (63%) and restricted formulary (24%). Drug safety (63%) and chances of adverse events (47%) were the most significant factors deciding treatment. Twenty-two percent (22%) reported 80–100% of CSU patients were complete responders to omalizumab; 34% preferred increasing frequency (q 2-weeks), and 18% preferred increasing dose (600 mg q 4-weeks) for partial or non-responders. UAS7, UCT, and CU-QoL were used to assess CSU by 55%, 29%, and 25% of respondents, respectively. Autoimmune thyroid disease (62%), thyroid abnormality (43%) and allergic rhinitis (35%) were the most frequent comorbidities reported.

Conclusions: Most clinicians favored omalizumab over other potential treatments due to safety. Although younger clinicians were more likely to prescribe omalizumab, cost and formulary access

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were major barriers. Only 22% of respondents reported 80% or greater of their patients had complete response to omalizumab, indicating the need for novel CSU therapies.

Keywords: Chronic spontaneous urticaria, Clinical research, Safety, Adverse effects, Monitoring, Biologics, H1-antihistamines, Epidemiology, Practice management, Alternative therapy

INTRODUCTION

Chronic spontaneous urticaria (CSU) is defined as "the spontaneous appearance of wheals, angioedema, or both for over 6 weeks, due to known or unknown causes."[1] The prevalence of CSU in the general population is estimated to be from 0.5% to 5%.[2] The average duration of an episode of CSU is between 2 and 5 years, with only 35%–50% experiencing remission within 1 year.[3] It has been demonstrated that CSU has a significant impact on affected patients' quality of life; 1 systematic review found CSU has been linked to depression and anxiety.[4] A clinical report describing the patient experience of having CSU divided the patient journey into 4 stages – Crisis, Searching for Answers, Diagnosis, and Disease Management.[5] Patients in that study described confusion, anxiety, and stress related to diagnosis. Economic impacts were also described, both with direct healthcare costs associated with treatment of CSU, and indirect costs such as days taken off work, recurrent healthcare utilization, and patient presentation to multiple subspecialists in the search for answers. Although the study focused on the United States, CSU occurs worldwide, and therefore international guidelines for treatment are published for use by allergists & immunologists globally.[1,6]

Urticaria and angioedema are caused by skin mast cell and basophil bioactive mediator release including preformed mediators such as histamine and newly-formed mediators such as leukotrienes, platelet activating factor, and cytokines.[2] Treatment revolves around the use of second generation non-sedating H1-antihistamine medications, which perform as inverse agonists to stabilize the inactive conformation of the H_1-receptor.[2] Although doses can be used up to 4 times the generally prescribed dosage of antihistamines, 1 systematic review found 63.2% of patients with CSU did not respond to standard dosages responded to this higher dose.[7] A treatment option for H_1 antihistamine-resistant CSU is omalizumab (Xolair), an IgG-anti-IgE antibody administered via injection. It was approved by the US Food and Drug Administration (FDA) in 2014 as well as the European Medicines Agency (EMA) for the indication CSU in adults and children at least 12 years of age. It is thought that omalizumab prevents IgE cross-linking of mast cells via binding to IgE thus preventing them from binding to FcεRI on mast cells, basophils, and other effector cells that bear these receptors. Phase 3 trials demonstrated that omalizumab decreased clinical signs and symptoms of chronic urticaria in those resistant to H_1 antihistamines.[8] Omalizumab allows allergists and immunologists to recommend a treatment option that spares patients from glucocorticoids and/or immunosuppressant medications, and is generally well-tolerated. Since its approval of omalizumab for treatment of CSU in 2014, there have been several real-world studies assessing its effectiveness. One retrospective study evaluated 298 omalizumab-treated patients in the United States to determine CSU patient clinical characteristics and treatment patterns treated with omalizumab.[9] The mean [SD] age of respondents was 43.5 [13.64] years; 70.8% were female and 84% were seen by an allergist/immunologist. All patients had $\geq$ 12 months of continuous treatment with omalizumab and a subset of patients (n = 138) had $\geq$ 18 months of follow-up on omalizumab. For patients with $\geq$ 12 months of follow-up 32.9% (n = 98) were on treatment by the end of the 18-month study. The mean number of continuous omalizumab treatment days was 443.1 (95% CI = 425.0–461.3). Omalizumab was discontinued in 98 patients over the entire 18-month study period but 28.6% restarted treatment within 329 days.[9] Overall, approximately 60% of patients remained on omalizumab beyond the 18-month study period. Use of medications such as oral glucocorticoids, montelukast, cyclosporine, and prescription H1 and H2 antihistamines decreased during the 1- to 6-month and 7- to 12-

month periods after starting omalizumab compared to baseline.[9] Another, previous smaller real world study demonstrated 72 of 86 patients demonstrated treatment response to omalizumab whereas 24.4% discontinued omalizumab. For all patients, use of oral glucocorticoids decreased post-treatment (52.3% vs 39.8%).[10] In a subsequent larger real-world study involving 1546 patients in the United States (mean ± standard deviation [SD] ages, 44 ± 14.5 years; 73.1% women), among the 84.5% initiated on omalizumab, 90% remained on the initial dose whereas 7.5% increased their dose and 4.6% decreased their dose. The mean ± SD treatment duration of omalizumab was 9.1 ± 3.8 months. The proportion of patients continuously treated with omalizumab was 67.3 after six months, 54.8 after nine months, and 47.4% after 12 months. Among the patients who discontinued omalizumab for ≥3 months (39.8%), 21% restarted the treatment after a mean ± SD of 4.4 ± 1.3 months.[11] In general, for all of the real-world omalizumab studies, the majority of treated patients demonstrated post-treatment effectiveness as measured by UAS7, improved quality of life and reduction of medication requirements including oral glucocorticoids.

Although the benefits of omalizumab have been well-demonstrated, it is unclear how prevalent usage of omalizumab is worldwide as healthcare systems vary significantly from free market to socialized systems, which are often underfunded and restrict use of biologics for treatment of many chronic illnesses, including CSU. Therefore, we developed a questionnaire survey that was distributed through the World Allergy Organization (WAO) to assess the diversity of practice patterns and behaviors of omalizumab, with the understanding that the use of omalizumab may not be as prevalent in some medical systems. This study was performed to understand these practice behaviors to potentially address healthcare inequities.

METHODS

Data were collected through electronic questionnaire surveys that queried WAO members worldwide regarding their treatment of CSU and usage of omalizumab. The questionnaire was initially developed by the study authors, and revisions were made based off review of the questionnaire by members of the WAO Urticaria Committee. Committee members also completed the electronic questionnaire to determine ease of use. WAO member responses were collected anonymously. The denominator for each response may vary as not all respondents answered each question resulting in missing data. All questionnaire data were deidentified and this study was given an exemption by a central institutional review board. Categorical data were analyzed for descriptive analysis using one-way frequency tabulation in SAS 9.4 (Cary, NC).

RESULTS

Demographics

Responses were received from 393 allergists & immunologists, and complete data were available for 348 respondents. Fig. 1 summarizes the countries of the respondents. Table 1 provides the number of respondents for each country that participated. Approximately 25% of respondents were from the United States. The average age of respondents was 51 but ranged from 28 to 90. Forty-eight percent of respondents were males, and 52% were female. Fifty-eight percent had over 15 years of clinical experience, while 10% had less than 5 years of clinical experience.

Specialties assessing CSU

Practice settings were varied with 42% working in private clinics or community practice, 36% in public hospitals, 24% in academia, and 18% in private hospitals. Among respondents, 347 were allergists of which 166 also practiced immunology; 22 were dermatologists. Among allergy specialists, 22 also practiced general internal medicine, 60 practiced pediatrics, and 13 pulmonary medicines. The number of patients seen by CSU clinicians saw each year varied from <25 to over 150 (Table 2).

Biomarkers and treatment decision

When asked if they used biomarkers to determine treatment decisions, 118 (39%) answered affirmatively; 106 (27%) used total IgE, 63 (16%) used thyroid peroxidase, 58 (15%) used C-reactive protein, 48 (12%) used ANA, 38 (10%) used a d-dimer, 40 (10%) used an autologous serum skin test, 14 (4%) used a chronic urticaria index, and 14 (4%) used a basophil activation test.

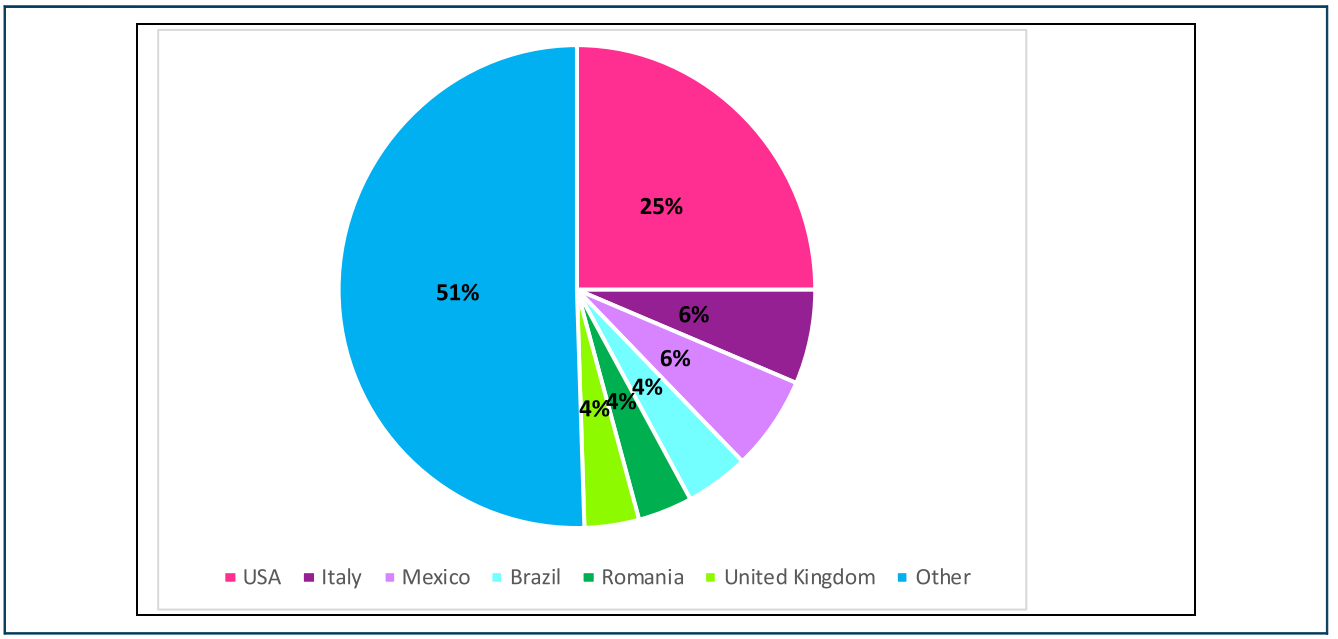

Fig. 1 Questionnaire Respondent's Countries of Origin (includes 4% response rate and above)

Use of patient reported outcome measures

Patient reported outcome measures to assess CSU such as the UAS7, UCT, and CU-QoL were used to assess CSU by 55%, 29%, and 25% of respondents, respectively. The most frequent comorbidities reported for their CSU patients were autoimmune thyroid disease (62%), thyroid abnormality (43%), and allergic rhinitis (35%).

Treatment approaches

Respondents used first generation antihistamines (FGAH) and second-generation antihistamines (SGAH) 22% and 88%, respectively, for the treatment of CSU. Eighty-two percent of respondents prescribed omalizumab for CSU patients (n = 321). This was highest among younger practitioners. The most significant barriers were cost

Algeria 1	Egypt 8	Italy 23	Peru 2	Sweden 4
Argentina 11	Finland 1	Japan 1	Philippines 2	Switzerland 2
Australia 11	France 1	Kenya 2	Poland 3	Thailand 3
Belarus 2	Georgia 3	Lebanon 2	Portugal 10	Turkey 13
Belgium 3	Germany 4	Lithuania 2	Qatar 2	Ukraine 1
Brazil 16	Greece 7	Malaysia 3	Romania 14	United Arab Emirates 2
Bulgaria 3	Honduras 1	Mexico 23	Russia 3	United Kingdom 13
Cambodia 1	Hungary 1	Moldavia 1	Saudi Arabia 1	Uruguay 2
Canada 12	India 10	Mongolia 3	South Africa 2	Vietnam 1
Chili 5	Indonesia 2	Netherland 2	South Korea 3	United States 93
China 1	Iran 2	New Zealand 1	Spain 7	
Columbia 5	Ireland 1	Pakistan 2	Sri Lanka 1	
Dominican Republic 3	Israel 3	Panama 2	Sudan 1	

Table 1. All countries with at least one respondent

Patients with CSU seen per year	Number (%)
<25	47 (12)
26–50	108 (27.5)
51–109	80 (20)
110–150	39 (10)
>150	81 (20)

Table 2. Number of CSU patients seen by each respondent per year

(63%) and restricted formulary meaning the use of omalizumab for CSU treatment was not available (24%). The most significant factors in deciding treatment were drug safety (63%) and chances of adverse events (47%). Forty-three percent prescribed omalizumab due to efficacy in clinical trials.

Most countries represented (n = 349; 89%) reported availability of omalizumab, the most frequent being United States, Italy, Mexico, Brazil, Romania, and the United Kingdom and 81% (n = 320) of respondents prescribed omalizumab. Countries in which omalizumab was reported not being available were Georgia (2 respondents), Romania, Sri Lanka, and Sudan. Countries in which respondents reported they did not know if omalizumab was available were Brazil (n = 1), Mongolia (n = 2), the United States (n = 1) (although all other respondents from the United States reported it was available), and 33 respondents did not answer if omalizumab was available in their country. Omalizumab was prescribed for CSU, Chronic Inducible Urticaria, and wheals with angioedema by 70%, 38%, and 34% of respondents, respectively. If patients were well-controlled on omalizumab, approximately 20% continued omalizumab for 12 months, 1.5% for 9 months, 28% for 6 months, and 4.8% for 3 months.

Only 22% reported 80–100% of CSU patients were complete responders to omalizumab; 7% reported 80–100% partial response to omalizumab. In terms of length of treatment to determine effectiveness for CSU, 49% recommended less than 6 months of treatment, 23% recommended 7–12 months of treatment, and 11% recommended over 12 months.

Interestingly, 20% of respondents continued omalizumab indefinitely. Approximately 50% of respondents were comfortable with patients self-administering omalizumab at home and 50% were not comfortable or unsure.

Guideline use

The majority of respondents (65%) used the international urticaria guideline (EAACI/GA^2 LEN/EDF/WAO Guideline)[1] in deciding treatment, whereas 16% used the US chronic urticaria guidelines (US Joint Task Force Practice Parameter), 7% used the UK guidelines, and 2% used the Canadian guidelines.

Insurance coverage of biologics

Expenses for biologics were covered by a national health system for 191 responders, 178 private insurance, 119 patient-paid, 55 independent co-pay assistance companies, and 16 reported other means of coverage. One hundred and fifty-four reported patients had no co-pay for biologics, 97 reported a fixed co-payment, and 84 reported a percentage. Most survey respondents could not approximate the flat co-payment rate, 33 reported they did not know, 25 reported >$20/month, 3 reported $11–20/month, and 10 reported <$10/month.

If omalizumab is ineffective in controlling CSU, 34% of respondents increased the frequency to every 2 weeks; with only partial response, 36% reported increasing the frequency to every 2 weeks. Only 18% routinely increased dosing of omalizumab to 600 mg every 4 weeks if recommended dosing did not provide complete control of CSU; 18% also increased the dose if patients were partial responders to omalizumab. If increasing dose or frequency, only 10% reported insurance always covered the increased cost, and 17% reported covering the cost with prior authorization or peer to peer review. Fourteen percent reported that insurance sometimes covered the increased cost, while 8% reported the increased cost was never covered by insurance. In terms of stepping down treatment, 20% reported reducing frequency first, then dosing; 13% reduced dose first, then frequency; 22% just reduced frequency and only 2% reduced dose. Sixty physicians (15%) reported just stopping the biologic completely and observing.

Alternative therapies

Approximately 26% and 29% of respondents used H2 antihistamines and leukotriene modifying agents as add-on therapies. When omalizumab was not effective or partially effective, several alternative medications were considered, but cyclosporine (47%) and chloroquine/hydroxychloroquine (17%) were the most used alternative agents used. Among those who used cyclosporine, 21% of patients had 80% or greater complete response as add-on or alternative agent. Twelve percent or fewer used methotrexate, colchicine, dapsone, mycophenolate, azathioprine, tacrolimus, sulfasalazine, tranexamic acid, danazol, phototherapy, vitamin D, IVIG, whole blood serum, dupilumab, and IL-1 beta.

Comorbid illnesses

The most common comorbidities in patients with chronic urticaria were autoimmune thyroid diseases (242 respondents, 62%), thyroid function abnormality (171 respondents, 44%), allergic rhinitis (138 respondents, 35%), psychiatric disorders (85 respondents, 22%), asthma (73 respondents, 19%), and low vitamin D (81 respondents, 21%).

DISCUSSION

To our knowledge, this is the first study to describe the practice habits of allergists and dermatologists using omalizumab for treatment of CSU worldwide. A previous study found that 63% of patients with CSU achieved complete control.[12] In that study, 33% of patients achieved complete disease control when either omalizumab or cyclosporine was added to an existing treatment regimen (data not available for only using omalizumab). Our study found that only 22% of allergists & immunologists surveyed found that 80–89% of their patients were complete responders to omalizumab (no hives after treatment). When using omalizumab in recommended dosing was not effective or partially effective, 70% of physicians increased the frequency, and 36% preferred to increase dose. This is a novel finding as limited data have been published on use of omalizumab outside of recommended dosing guidelines. We gathered similar data in terms of stepping down omalizumab therapy after achieving control, with 20% reducing frequency first, then dosing, and 13% reducing dosing, then frequency, and 15% completely stopped the biologic altogether without stepdown therapy. In terms of length of treatment, the majority (49%) in our study recommended less than 6 months of therapy; it is unclear if this is long enough to prevent future episodes. Additionally, further studies are needed on stepdown therapy, if one method (stepping down by dose, frequency, or both) is more effective or provides a longer length of remission than others.

Although omalizumab may not provide a complete response to CSU, it is indisputable that it has been a useful and widely used therapy in the treatment of CSU. It is important to note that omalizumab is not available in all countries, and some physicians did not know if it was available in their country. This demonstrates a global inequity in access to certain treatments and therapies. For example, although Romania was found to be 1 of the countries in which omalizumab was most frequently used, 1 physician from Romania reported not having knowledge of availability. Although it has been demonstrated that it can take 1.4 $\pm$ 2.7 years[12] to potentially obtain complete remission of CSU, omalizumab should be offered as an option for treatment to those resistant to initial therapy with antihistamines. This is recommended in the Joint Task Force Practice Parameter as well as the international EAACI/GA^{2}LEN/EDF/WAO guidelines for the definition, classification, diagnosis, and management of urticaria.[1,2]

It is promising that omalizumab is available in a wide variety of countries, but the fact that some are excluded demonstrates that there are still limitations to access of healthcare in some countries which has been reported for biologics and treatment of asthma in the United States.[13] Surprisingly, 119 reported that patients paid for their own therapy; depending on the healthcare system, this may represent a significant cost and large barrier to access to omalizumab in some patients who do not have these resources. Many survey respondents were unable to estimate the cost to patients when prescribing omalizumab. There also was not a consensus on insurance payor status of coverage if increased dosage or frequency is trialed due to lack or ineffective response. It was reported that 17% of physicians had to complete peer-to-peer

discussions, which can take significant resources and time away from patients.

Interestingly, our study found a larger than expected number of patients with autoimmune thyroid disease or thyroid dysfunction (62% and 44%, respectively). One recent study has been published demonstrating that thyroid autoimmunity is not associated with omalizumab response.[14] More patients had associated thyroid dysfunction than allergic rhinitis (35%), asthma (19%). Many patients also had low vitamin D (21%). The large amount of patients with thyroid-associated urticaria indicates that it may be worthwhile for physicians to screen CSU patients with new-onset urticaria for thyroid deficiency and thyroid autoimmune disease as part of their initial evaluation currently not recommended by guidelines.[1,15] Similarly, given the strong association between a low Vitamin D level and CSU one should also consider assessing for low vitamin D although a previous meta-analysis and systematic review emphasized low evidence showing causation of vitamin D deficiency and CSU even though supplementation seemed to show some efficacy indicating the need for further well designed randomized controlled trials to confirm this relationship.[16]

Strengths of this study include the wide variety of geographic diversity available in survey responses as well as the large number of questionnaire responses available. Additionally, other therapies aside from omalizumab were assessed, as well as prescribing habits of using omalizumab. This is also a novel study on barriers to using omalizumab. Limitations include that as this was a questionnaire study, there is the possibility of recall bias. Additionally, some physicians did not respond to the survey, or did not respond to all questions, creating the possibility of non-response bias. Despite these limitations, we still feel this study provides useful and novel information regarding global practice habits in the use of omalizumab in treatment of CSU.

It is also clear that a need exists for additional therapies for CSU. A recent clinical management review discussed alternative therapies for treatment of CSU, including anti-inflammatories, alternative biologic medications, and immunosuppressive medications.[17] It is promising that studies are underway for treatment of CSU, as the length of time to resolution and impact on quality of life can be distressing for patients.

Abbreviations
CSU, chronic spontaneous urticaria; UAS, urticaria activituy score; WAO, world allergy organization; VIG, intravenous immunoglobulin.

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Author's contributions
All authors contributed to the questionnaire design, interpretation of data, writing and editing of the manuscript. All abided by ICMJE policies.

Ethics statement
This questionnaire study was exempted by a central IRB.

Declaration of competing interest
CJR, RA, TC, AG, HL, EM, ET, DNV – nothing to declare.
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